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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	PDC 119	8907

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EXAMINER
SHEIKH, HUMERA N

ART UNIT	PAPER NUMBER
1615	18

DATE MAILED: 07/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/766,362	STEINER ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Receipt of the Amendment filed 04/29/03 is acknowledged.

Claims 1-19 are pending. Claims 1, 7 and 14 have been amended. Claims 1-19 remain rejected.

Claim Rejections - 35 USC § 112

Claims 1, 7 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "including" in claims 1, 7 and 14, lines 11 and 15, is considered indefinite because the term "including" is not proper as stated since the applicant recites a specific listing of materials in a Markush group format and hence the term "including" would not be appropriate and renders the claim indefinite. Only the specified materials should be recited in the Markush listing. It is suggested that the term "including" be cancelled.

Claims 1, 7 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "diketopiperazines" in claims 1, 7 and 14, line 5, is indefinite and confusing since diketopiperazine, which is a drug, is listed amongst a list of polymers. Since diketopiperazine is not a polymer, but rather a drug, the term "diketopiperazines" in the group listing of polymers renders the claims indefinite. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-11 and 13-17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Illum (US Pat. No. 5,690,954).

Illum discloses a drug delivery system for nasal administration of an active drug wherein the drug delivery system comprises microsphere particles formed of an active drug and polymeric materials whereby the composition is administered in the form of a

dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 4, lines 5-35); (col. 5, line 14 through col. 6, line 28).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US Pat. No. 5,690,954) in view of Camden (US Pat. No. 6,136,835).

Illum, as discussed above, teaches a drug delivery system for nasal administration of an active drug wherein the drug delivery system comprises microsphere particles formed of an active drug and polymeric materials whereby the

composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 4, lines 5-35); (col. 5, line 14 through col. 6, line 28).

The particulate drug delivery system for administration of an active drug comprises microspheres, which include an effective amount of the active drug and an absorption enhancing material associated with each microsphere which enhances passage of the active drug through a membrane and increases the bioavailability of the active drug (claim 1).

Preferably, the particles are administered in the form of a powder by spraying and have bioadhesive properties. The microspheres should be of a size between 10 and 100 microns and prepared from a biocompatible material. Suitable materials include, starch, gelatin, casein, dextrans, albumin, collagen, alginates, polyvinyl acetate, etc (col. 6, lines 13-28).

Illum teaches that the drug to be administered to a mucosal surface such as the nose, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system. The advantage of using bioadhesive microsphere systems for administration to the mucosal surface is that such systems allow a longer period of contact, especially if the microspheres are slowly degrading. This is particularly true for the nasal administration of drugs contained in microspheres produced from natural materials such as albumin, gelatin and starch (col. 5, line 14-26).

Additional suitable drugs that can be used are anti-inflammatory agents, vasoconstrictors and antihistaminic agents, such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine. The microspheres can be administered via the nasal route using a nasal insufflator device (col. 8, line 44 through col. 9, line 60).

Illum teaches microspheres having a particle size of between 10 and 100 microns. The instant claims require an average particle size of between 10 and 20 microns. The range taught by the prior art, is a broader range, which reads on the applicant's claimed range of 10-20 microns.

Illum's patent is deficient only in the sense that it does not explicitly teach a drug which is formulated in a diketopiperazine formulation.

Camden teaches a method for the treatment of viral infections comprising a diketopiperazine derivative in combination with another compound or derivative, wherein the composition can be suitable for nasal administration and comprises a powder having a particle size of less than about 100 microns, preferably less than about 50 microns (see reference col. 13, lines 20-32); (col. 16, line 61 through col. 17, line 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Camden within the teachings of Illum because Camden explicitly teaches the use of a diketopiperazine derivative in the form of a powder, suitable for nasal administration wherein the powder has a particle size of less than about 100 microns and more preferably, less than about 50 microns and Illum teaches a particulate drug delivery system comprising particles having a

particle size of between 10 and 100 microns whereby the composition can be nasally administered and in the form of a dry powder. The expected result would be an improved particulate formulation for nasal application that provides suitable drug retention in the nasal region.

Response to Arguments

Applicant's arguments filed 04/29/03 have been fully considered but they are not persuasive.

Firstly, the applicant argued regarding the 35 USC 102(b) rejection over Illum stating, "Illum fails to teach a dry powder formulation containing microparticles formed of a drug and a polymer as defined in any of claims 1-19. The microspheres are formed of a material, which do not fall within the definition of polymers as defined in any of claims 1-19.

These arguments have been fully considered but were not found to be persuasive. The instant invention is drawn to a composition for nasal administration of a drug in a dry powder form having an average particle size of between 10 and 20 microns. The dry powder form contains microparticles comprising the drug and a material that can be a diketopiperazine or a polymer defined therein. Illum discloses a drug delivery system for nasal administration of an active drug wherein the drug delivery system comprises microsphere particles formed of an active drug and polymeric

materials whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 4, lines 5-35); (col. 5, line 14 through col. 6, line 28). Illum at column 6, lines 29-54, teaches the production of starch microspheres comprising a solution of polyethylene glycol. As such the prior art clearly meets the instant claim language which requires the presence of particular polymeric materials. The applicants argument that Illum teaches microspheres that are preferably formed of starch, gelatin, casein, dextrans, etc. has been considered, but was not persuasive since the instant claim language is "comprising" language and as such, the "comprising" claim language does not exclude other components or materials such as starch, gelatin, casein, etc. as taught by Illum.

Secondly, the applicant argued regarding the 35 USC 103(a) rejection of claims 5, 12 and 18 (Illum in view of Camden), stating, "Camden does not teach a dry powder formulation comprising the drug and the bis-diketopiperazine alone without a solid carrier. Camden does not recognize or teach the size range of 10 to 20 microns for delivery of the formulation to the desired nasal region."

These arguments have been fully considered but were not found to be persuasive. Camden teaches teaches a method for the treatment of viral infections comprising a diketopiperazine derivative in combination with another compound or derivative, wherein the composition can be suitable for nasal administration and comprises a powder having a particle size of less than about 100 microns, preferably less than about 50 microns (see reference col. 13, lines 20-32); (col. 16, line 61 through

col. 17, line 4). The instant "comprising" claim language does not exclude the use of additional components asides from those recited in the claims. Thus the teaching of a carrier in combination with the drug and the bis-diketopiperazine as taught by Camden still applies and reads on the instant claim language.

The applicant also argued, "Illum in view of Camden failed to disclose every element of the composition and method of using the composition defined in any of claims 1-19. None of Illum and Camden teaches the desirability of avoiding formulations of a particle size less than 10 microns. Moreover, Camden teaches formulations having a particle size less than 50 microns, which encompasses formulations having a particle size in the range between 0 and 10 microns, in the case of an antihistamine, results in a bitter taste of the drug. Therefore, Illum in view of Camden would not provide the motivation to make and use the composition as defined. Illum in view of Camden fail to teach one of ordinary skill in the art with "sufficient specificity" to lead one of ordinary skill in the art to expect that nasal formulations of drug particles having a size of below 10 microns would give a lower efficiency of drug delivery."

These arguments have been fully considered but were not found to be persuasive. The prior art teaches a dry powder composition wherein the particles have a size of between about 10 microns to about 100 microns (Illum) and less than about 100 microns, preferably less than about 50 microns (Camden). This range clearly meets the instantly claimed range of between 10 and 20 microns. The prior art teaches that the composition is a powder formulation suitable for nasal administration with a

particle size of about 10 to 100 microns, or less than 50 microns. Furthermore, one of ordinary skill in the art would be well aware of the advantages or disadvantages of utilizing a particular micron size, based on the intended purpose and in order to obtain the best possible results. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Illum discloses a drug delivery system for nasal administration of an active drug wherein the drug delivery system comprises microsphere particles formed of an active drug and polymeric materials whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns. Illum is lacking only in the sense that he does not explicitly teach a drug which is formulated in a diketopiperazine formulation. Camden was relied upon for the teaching of a formulation comprising diketopiperazine derivative in combination with another compound or derivative, wherein the composition can be suitable for nasal administration. There would be ample motivation for one of ordinary skill in the art to use the combined teachings of Illum and Camden to arrive at a similar formulation as instantly claimed. The prior art clearly teaches a powder formulation for use through the nose, with particle

sizes that meet the applicant's desired ranges. Hence, the instant invention is rendered unpatentable over the combined teachings of Illum and Camden.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns
July 07,2003

THURMAN K. PAGE
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